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**The Human DNA Repair Protein XRCC1 is a Nuclease**

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*XRCC1* is required for the repair of single-strand breaks resulting from DNA base damage, but the precise function of the protein is unknown. Recent studies have demonstrated that the absence of XRCC1 protein during mouse embryogenesis is lethal, and moreover that the protein directly interacts with Polymerase β and DNA ligase III, and also perhaps with poly(ADP-ribose) polymerase, proteins that act in the base excision repair pathway (Caldecott et al (1996) Nucleic Acids Res. 24:4387-94). To determine the function of XRCC1, we expressed the protein from a bacterial vector that adds short peptide affinity tags to both termini. Fusion of the 15aa Ribonuclease-S peptide to the N-terminus of XRCC1 resulted in a significant increase in the level of soluble protein expressed. Affinity capture of the protein followed by gel filtration resulted in purified protein. XRCC1 catalyzed the release of nucleotide from untreated or nicked duplex DNA, but not from denatured (ss) or depurinated DNA. That this duplex-specific activity is an intrinsic feature of the XRCC1 protein was demonstrated by an in-gel activity assay following denaturing electrophoresis. The XRCC1 amino acid sequence shares significant similarity with the cell cycle proteins Dpb11 (*S. cerevisiae*), rad4/cut5 (*S. pombe*), and p53 (human). From these new data we propose a critical function for the XRCC1 nuclease in an accessory role to Pol β that acts in the final stage of the base excision repair pathway and that is essential for maintaining the integrity of the genome. Work was done under the auspices of the U.S. DOE by LLNL under contract No. W-7405-ENG-48.